The Immunologic Staging of Chronic Active Hepatitis B Patients in Hawaii

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The hepatitis B antigen/antibody levels and natural killer cell activity status of chronic hepatitis B patients identified by the Hawaii State Department of Health were evaluated to select chronically infected hepatitis B patients for interferon therapy and to determine possible immunodeficiencies. The presence of hepatitis Be antigen denotes active replication of the virus. Ninety-five patients were studied: 17/95 (18%) had chronic active hepatitis B, 71/95 (75%) were hepatitis B carriers and 7/95 (7%) had seroconverted. NK activity to the erythroleukemia K562 cell and virus-infected HSV-1 cell of the chronic active and carrier population (P<.05) were lower than that of the control population and those who had spontaneously seroconverted. Of this population 18% were identified with active viral infection and would be candidates for interferon therapy.

Introduction

Infection from the hepatitis B virus (HBV) presents Hawaii with a major public health problem because of its large immigrant population from Asia and the South Pacific. The HBV–carrier rate in Hawaii is estimated at 2% to 3% as compared to the overall U.S. rate of 0.5%.[1]

HBV is a double-stranded DNA virus with 3 different protein antigenic markers: Hepatitis B core antigen (HBcAg), hepatitis B surface antigen (HBsAg), and the core–related antigen, hepatitis Be or (HBeAg).[2] HBsAg is found on the surface or the envelope of HBV. The inner coat, the capsid, is a single core protein surrounding the viral DNA where HBcAg is displayed.[2] Although HBV is doubled-stranded, the plus strand is shorter than the minus strand. The missing piece in the plus strand exists outside of the virus as a viral fragment, HBe antigen (HBeAg). Therefore, if HBeAg is detected, there is active HBV replication occurring in hepatocytes. HBV carriers are patients who demonstrate persistent hepatitis B surface antigenemia. The presence of active viral replication in hepatocytes will be indicated by finding serologic HBe antigen. Carriers do not have antibody to the HBsAg.

The immunomodulating and anti-viral effect of interferon (IFN) has been demonstrated to be effective in up to 50% of chronic, active hepatitis B patients.[2-6] The FDA approved interferon therapy for HBeAg–positive patients in July 1992.

NK cells, large granular lymphocytes, are considered important in natural immunosurveillance in cancer and certain infectious diseases.[10] NK–cell cytotoxicity does not require prior exposure to antigen and is not MHC restricted. We evaluated the hepatitis B antigen/antibody levels and immunological status of volunteers from the registry of the Hawaii Department of Health to select hepatitis B patients for long-term interferon therapy and to determine the possible deficiencies in natural killer cell activity in these patients.

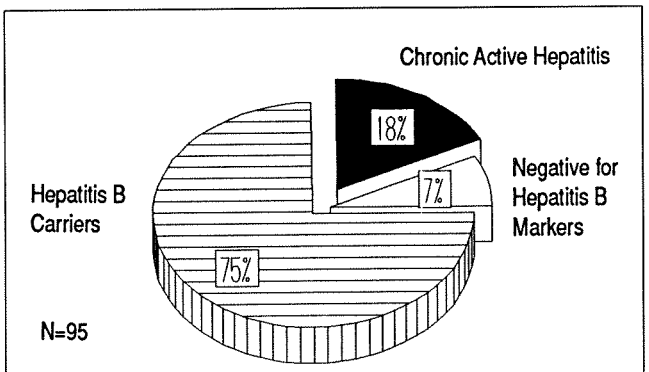

Figure 1 Categorization of study population. Three groups were delineated. The chronic hepatitis B group will be amenable to interferon therapy.

Methods and Material

Patient Population.–The Epidemiology Branch of the Hawaii State Department of Health contacted patients with chronic hepatitis B who were registered in its HBV program to obtain patient permission to be retested and staged for possible therapy with interferon alpha-2b. Patients replying in the affirmative were contacted and scheduled for evaluation of their hepatitis Be antigen/antibody status and retesting of their hepatitis B surface antigen/antibody status and serum ALT(SGPT) levels. Information on birthplace, ethnicity and other standard demographic data were obtained from each patient; all patients signed informed consent forms. HBsAg and antibody to HBsAg (anti-HBs) were performed at St. Francis Medical Center, while HBeAg and anti-HBe were performed by SmithKline Beecham

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Laboratories, both using diagnostic materials by Abbott Laboratories, North Chicago, Illinois.

Immunological Evaluation.–Natural killer cell activity (NK) to the K562 erythroleukemia cell and herpes simplex virus–infected fibroblast cell were analyzed in the first 50 patients. Standard chromium-release cytotoxic assays were performed with Ficoll-Hypaque–separated peripheral blood mononuclear cells as previously reported.[7-9] The controls were healthy volunteers who were recruited from the laboratory, medical center and community organizations.

Statistical Analyses.–Data was analyzed utilizing the PC Stat program from Human System Dynamics, Northridge, California. NK activity was analyzed using the Mann-Whitney non-parametric test. Data is reported as the mean ±1 SD.

Results

This report defines chronic, active hepatitis B patients as those with HBsAg and HBeAg, without anti-HBe and anti-HBs. Chronic hepatitis B carriers are defined as those patients who are HBsAg–positive, anti-HBs negative and anti-HBe positive in response to their hepatitis infection. (Table 1) Ninety-five patients agreed to be considered for the study: 17/95(18%) had chronic, active hepatitis B, 71/95 (75%) were hepatitis B carriers and 7/95 (7%) had no remaining evidence of hepatitis B markers. (Figure 1)

Sixty-one women and 27 men were positive for hepatitis B. The same women–to–men ratio was observed in the chronic, active and carrier groups. The chronic, active hepatitis B group was younger than the carrier group, averaging 32 years of age as opposed to the carrier group, which averaged 39 years, P=<.04.

Table 1 Staging Hepatitis B

Population	HBeAg	anti-HBe	HBsAg	anti-HBs
Chronic Active Hep B	+	-	+	-
Chronic Hep B (Carrier)	-	+	+	-

Table 2. NK activity of chronic Hepatitis B Patients (X±SD)

	N	K562 20% (lu)	N	HSV-1 20% (lu)
Control	31	100 ±76	31	48 ± 35
Hep B-Active	12	78 ±55	10	48 ± 45
Hep B-Carrier	23	69 ±54*	23	34 ± 33**

(lu): Mean lytic units is defined as the number of effector cells/10E+7 required to achieve 20% lysis of the target cells of NK activity of blood lymphocytes.

Mann-Whitney Non-parametric Analysis.
*p<.05 **p<.02

The major ethnic distribution of the entire group studied consisted of the following: Filipino (33%), Chinese (17%), Vietnamese (12.5%), Japanese (10%), mixed Asian (8%), and Korean (6%). Most of the Filipinos and Vietnamese were not born in the United States; some of the Chinese and Japanese were born in Hawaii. These same 5 races predominated in the active hepatitis group. No active patients were identified in the Samoan, Polynesian, Laotian, Caucasian or mixed ethnic groups. We could not accurately determine when the patients were initially infected.

Serum ALT (SGPT) levels were elevated in all except 2 of the chronic active hepatitis B patients, X (mean) = 100 ±128. Only 3/71 (9%) hepatitis B carriers had ALT level >1.3x high normal value.

NK Activity.–Mean values of NK activity (lytic units in 20% Kill) to the K562 erythroleukemia cell line were 100 ±82 lytic units in the control individuals, but lower, 78 ±55 lytic units in the chronic active hepatitis B and 69 ±54 lytic units in the carrier hepatitis B group. (Table 2) A significant difference was noted with non-parametric analysis for NK (K562) activity (P<.05) and for NK (HSV-1) activity (P<.02). The patients who had spontaneously seroconverted had NK(K562) activity of 146 ±72, not significantly different from that of the controls.

Discussion

Previously diagnosed chronic hepatitis B patients were screened to delineate patients who would qualify for therapy with recombinant interferon alpha-2b. We have identified a high 18% incidence of chronic active hepatitis B in this population. This is the stage of the disease that has been reported to respond to therapy with long–term interferon alpha-2b.

The typical patient in this study was a young woman with responsible employment or who was raising a young family. Also of significance was the preponderance of patients of Asian descent who primarily were immigrants and some of the Chinese and Japanese who were born in Hawaii.

Young hepatitis B patients should be treated to prevent the development of cirrhosis and/or hepatoma in the future. The State of Hawaii has developed a successful hepatitis B vaccination program in the newborn population. Efforts and attention should also be directed to immigrants arriving in Hawaii from areas of the world endemic for HBV.

As licensed by the FDA, interferon is administered at 5 million units daily or 10 million units 3 times a week for 4 months. Fatigue, a side-effect of interferon at these levels, generally is significant, which might influence the productivity of these patients over long periods. Therapeutic trials must be designed to allow these patients to function normally.

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rate was 50% should perforation occur. Cancer Research Center of Hawaii director, **Brian Issell**, reported that during his 5 years at Stanford, the incidence of perforation had been very low. Dennis wondered if surgery was contraindicated anyway because of the omental and peritoneal adenopathy. Scott could not commit himself without first reviewing the scans personally.

Moderator **Ken Sumida** summarized: "Apparently everyone will go along with chemotherapy without a total gastrectomy." For once, everyone was in accord.

Novel treatment

(By James Watt Toronto, *Punch*, June 1993)

A long time ago when I was an intern at a Toronto teaching hospital, a patient came to emergency with a fish bone stuck in her throat. The ENT staff physician on call was contacted and the intern was told to take the patient to the ENT operating room.

Just outside emergency was a corridor with a gently sloping ramp leading to another part of the hospital where the ENT OR was located.

At the top of the ramp, the intern lost control of the wheelchair, and it hurtled down the ramp. At the bottom of the ramp, one of the wheels of the wheelchair caught on the doorway and the patient was thrown to the ground. The patient immediately coughed up the fish bone.

With great presence of mind the intern said, "You're awfully lucky, lady—usually we have to do this 2 or 3 times before we get it out."

Oncology conference

(December 9, 1993)

Former KMC pathologist emeritus **Grant Stemmerman** (Now working out of Cincinnati) spoke on his favorite subject "Intestinal metaplasia and gastric cancer."

Oncologist **Kaye Kawahara** presented a 52-year-old Filipino man who had stopped smoking 10 years before but had a T3 lesion of the larynx when worked up for persistent hoarseness by ENT **Meredith Pang**. Radiologist **Howard Arimoto** showed CT scans of the lesion. Moderator **Lois Mastrofrancesco** asked Stemmy the probability of cancer after quitting smoking more than 10 years. Stemmy remarked that the probability curve was still quite high. He added, "Filipinos have the lowest cancer incidence in Hawaii because of their high vegetable diet. It is remarkable that he does have cancer." Kaye explained that this Filipino man was a robust meat eater and did not like his veggies.

Lois, a quality-of-life advocate, explained that traditionally larngeal Ca was treated with laryngectomy followed by chemo or radiation; now the trend is larynx preservation when possible viz chemo and radiation first and if this fails, laryngectomy. The survival curves are the same.

Do unto others

(James Fisher, Jr.)

▲ "To have a friend, you must be a friend, starting with yourself."

▲ "The greatest virtue is kindness. You can't love everyone, but you can be kind to everyone."

▲ "Be enthusiastic. Nothing of consequence was ever achieved without enthusiasm."

▲ "Be positive. Positive people attract others while negative people repel."

(From *Readers Digest*, June 1993)

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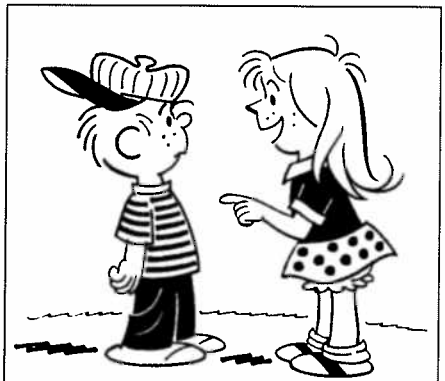

"LET'S PLAY DOCTOR. I'LL BE THE DOCTOR AND YOU BE THE MALE NURSE."